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PhRMA

August 23, 2004

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2004S-0233; Solicitation of Comments on Stimulating Innovation in Medical Technologies

Dear Sir/Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) welcomes the opportunity to provide input in response to the Department of Health and Human Services' (HHS) notice soliciting comments on stimulating innovation in medical technologies. 69 Fed. Reg. 29544 (May 24, 2004) (Docket No. 2004S-0233) (Notice). PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to lead longer, healthier and more productive lives. Investing more than $30 billion annually in discovering and developing new medicines, PhRMA companies are leading the way in the search for cures.

Discovering and developing innovative new drug products has always been a difficult, risky and uncertain undertaking. Yet over the past decade, pharmaceutical companies have pushed the scientific envelope, working at the cellular and molecular levels to dramatically advance the treatment of disease. At the end of 2002, 28 percent more investigational new drug applications (INDs) were active under commercial sponsorship than was true one decade before. Food and Drug Administration, "Number of Active INDs at the Close of the Calendar Year," 19 March 2003 http://www.fda.gov/cder/rdmt/cyactind.htm (5 August 2003). More than 1,000 medicines are now in the development pipeline. *New Drugs in Development* series (Washington, DC: PhRMA, 2001-2003).

Between 1993 and 2003, more than 300 new drugs, biologics, and vaccines that prevent and treat over 150 conditions were approved by the Food and Drug Administration (FDA). *New Drugs Approvals* series (Washington, DC: PhRMA, 1994-2003). The FDA also gave the go-ahead for numerous new indications for previously approved medicines, allowing physicians to tailor treatment strategies to meet a patient's individual disease status, past medication history, side effect tolerance, and

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preferences. The new medicines that are the product of this decade of innovation have dramatically changed the "standard of care" for several major conditions, including rheumatoid arthritis, human immunodeficiency virus (HIV) infection, Parkinson's disease, diabetes, schizophrenia, cancer, cardiovascular disease, and many others.

These advances have resulted in significant progress against many of the most serious diseases and conditions we face. In 2003, then-FDA Commissioner Mark McClellan, M.D. described well this progress: "Over the last century, the value of gains in life expectancy seen in the US is greater than the total value of all the measured growth in our economic output. New drugs are no small part of this medical miracle. The reduction in US mortality from cardiovascular disease alone has been valued at $1.5 trillion annually during from 1970 to 1990. Mark McClellan, former FDA Commissioner and current CMS Administrator, in presentation to the First International Colloquium on Generic Medicine, September 25, 2003.

Likewise, Columbia University researcher Frank Lichtenberg found that in the Medicare population, for every additional $1 spent on new drugs, non-drug expenditures are reduced by $8.38, resulting in savings of $7.38. F Lichtenberg, "Benefits and Costs of Newer Drugs: An Update," National Bureau of Economic Research Working Paper No. w8996 (Cambridge, MA: NBER, June 2002).

Despite the huge successes of the past decade in discovering innovative treatments for seemingly intractable diseases, the scientific and regulatory barriers to innovation have also grown. Throughout the decade, pharmaceutical companies have shifted research to more complex diseases, clinical trial failure rates have remained high, and a rigorous regulatory environment has prevailed. The result of these growing demands on drug development has been an escalation in the cost to develop new drugs and rising difficulties in bringing promising new drug candidates to market. As HHS notes, current estimates suggest that it takes 10 to 15 years and $800 million to bring a single drug product from the laboratory to the patient's bedside.

In light of these barriers, HHS' current effort to explore strategies within and among HHS and its constituent agencies to accelerate the discovery and development of innovative new medical technologies is extremely important. PhRMA and its member companies, which are on the front lines of this critical fight, appreciate the opportunity to provide comments. Although much work remains to be done, PhRMA believes that HHS can significantly improve the environment for innovation by focusing on the following areas:

1. Fully support FDA's *Critical Path* initiative;

2. Facilitate collaboration between FDA, the National Institutes of Health (NIH), industry and other stakeholders in identifying and validating useful biomarkers;

3. Encourage NIH to expand its basic research into diseases that currently are not well-understood;

4. Facilitate research into treatments and diagnostics for primary prevention by removing existing regulatory barriers and ensuring adequate reimbursement by insurers and government programs;

5. Support payment policies that encourage continued innovation; and

6. Educate the public and policymakers about the drug discovery process and the need for policies that encourage innovation.

1. Full Departmental Support for FDA's Critical Path Initiative

One of the most important actions HHS can undertake to spur innovation is to ensure that FDA' *Critical Path* initiative is fully supported at the Departmental level, adequately funded to accomplish its goals, and well coordinated with other similar initiatives within HHS. Because FDA stands at the gateway between the research laboratory and the patient's bedside, FDA is uniquely positioned to understand the scientific and regulatory hurdles associated with bringing innovative medicines to the marketplace. PhRMA supports FDA's initiative to join with its stakeholders to think creatively about translational and "critical path" research and its potential impact on pharmaceutical development and the regulatory review process. Given the FDA's unique position and existing initiative in this area, PhRMA believes that FDA's *Critical Path* initiative should be a primary focus of HHS' efforts to encourage innovation.

In addition to supporting FDA's *Critical Path* initiative administratively, HHS should ensure that FDA's initiative has adequate funding to accomplish its important short-term and long-term goals. Without adequate funding, FDA's *Critical Path* initiative is unlikely to be able to deliver on its promise to spur medical innovation for future generations.

Finally, HHS is well-positioned to ensure that other similar initiatives, such as NIH's *Roadmap for Medical Research* (*Roadmap*), are coordinated and integrated with FDA's *Critical Path* initiative. Given the government's limited resources in this area, it is important to avoid costly and duplicative work by separate government agencies. HHS should seek to ensure that the government's limited resources are maximized by coordinating work between its agencies according to their respective missions and areas of expertise.

In this regard, PhRMA was pleased by the Department's May 19, 2004 announcement of the formation of a taskforce on medical technology innovation to be led by Dr. Lester Crawford, Acting FDA Commissioner. Formation of the taskforce is commendable first step in coordinating the activities of HHS' operating agencies. Industry supports the goals of the taskforce, which is to look for opportunities across HHS to streamline and promote faster access to new innovative medical technologies. Also, we applaud Dr. Crawford's announcement of a series of public round tables in September to help streamline and promote faster access to new technologies. The PhRMA member companies offer their support in planning these meeting and welcome the opportunity to actively participate in the meeting discussion. We also look forward to participating in the activities of the Centers for Medicare and Medicaid Services' (CMS') Council for Technology and Innovation.

2. Facilitate Collaboration On Biomarkers

HHS should facilitate collaboration between FDA, NIH, industry and other interested stakeholders on the identification and validation of biomarkers and surrogate endpoints.

As discussed above, the pathway for approving a new medical technology is long and arduous, often requiring multiple clinical trials demonstrating that the drug product has a positive effect on a clinical endpoint such as mortality, i.e., that it increases survival. While this should be the ultimate goal of any treatment, it is often difficult, costly and time-consuming to prove. The increased use of biomarkers and surrogate endpoints would streamline clinical testing and approval pathways for many drugs, bringing needed treatments to patients faster and more economically, and improving patient outcomes. For example, reliance on surrogate endpoints such as CD4 cell counts and, later, viral load, helped spur the development and approval of a multitude of new medications to treat HIV infection in the 1990s, transforming HIV infection from

a ruthless killer in the 1980s into more of a chronic disease that now can be managed with appropriate medication regimens.

While many PhRMA member companies have and will continue to work individually on identifying and validating appropriate surrogate endpoints, PhRMA believes that collaborative efforts between FDA, NIH and industry can play an important role. FDA brings a unique perspective as the agency component responsible for approving innovative pharmaceutical products. Likewise, NIH is well situated to perform the necessary research and analysis to validate appropriate biomarkers and surrogate endpoints. However, there needs to be close coordination between NIH, FDA and industry stakeholders to ensure that appropriate candidates for study are chosen and that NIH research meets the regulatory needs of FDA and industry.

An important practical consideration in the validation of biomarkers is the accumulation of sufficient data, preferably from multiple sources, to demonstrate a persuasive statistical or evidentiary case. In principle, PhRMA would be interested in exploring creative ways to do this, for example:

- With appropriate incentives and safeguards for data confidentiality, groups of sponsors might consider pooling experimental data for analysis by a third party, who could then prepare a case for presentation to the Agency. This is a precedented model, having been used in the validation of RNA copy number as a surrogate endpoint for the efficacy of drugs to treat AIDS/HIV.

- Similarly, it may be appropriate for cross-institutional, multidisciplinary work groups to be established to study the design and validation of compound biomarkers made up of multiple simultaneous or correlated biological events or findings. This approach would be particularly appropriate in situations where the availability of such a biomarker would be an important aid to drug development and where there is a reasonable chance of a favorable validation outcome. FDA could be an important facilitator in this biomarker validation process.

In short, PhRMA believes that, while a collaborative model is not always necessary, it could be useful in many cases to spur development and regulatory acceptance of appropriate biomarkers and surrogate endpoints. It is not clear exactly what form such a collaborative model would take, but PhRMA is committed to help explore this concept in more detail through additional conversations with HHS, FDA and NIH and through public dialogue, such as proposed public meetings.

3. Basic Research by NIH

Another important action that HHS can pursue to spur innovation is to encourage NIH to expand its basic research into diseases that currently are not well-understood. PhRMA believes that there is a need for basic research into the mechanisms of disease progression for many dangerous and debilitating diseases. For instance, there are many diseases, such as osteoarthritis and Alzheimer's disease, for which we have very little understanding of how or why the disease progresses, i.e., its mechanism of action.

This lack of basic knowledge makes it difficult for industry to develop innovative drug products to treat these diseases and creates barriers to innovation. Basic research aimed at understanding disease progression could spur industry research into innovative treatments by identifying new targets or new mechanisms to attack. For example, basic research into the molecular characterization of lymphomas permitted researchers to identify specific tumor types using cell surface markers which resulted in the development of new cancer treatments directed at these specific tumor types.

NIH is perfectly situated to fund and/or conduct this type of basic research and, in fact, already conducts much of it. However, there is still a need for much additional basic research, and PhRMA believes that NIH's efforts in this area can and should be expanded. Such research should be conducted in consultation with FDA and industry stakeholders to ensure it is focused on relevant disease states and is not duplicative of work already being conducted by other researchers.

4. Facilitate Research Into Diagnostics and Treatments for Primary Prevention

For many diseases, such as cancer, the most cost-effective treatment may be prevention. Yet few products for prevention ever reach the market because of significant regulatory, reimbursement and other barriers. For instance, prevention studies typically involve more subjects and take significantly longer than studies for disease treatments, and, once approved, products intended for prevention often face hurdles in being reimbursed at an appropriate level.

HHS and its components could help spur innovative research into diagnostics and treatments for primary prevention by clarifying and streamlining the regulatory requirements for approval. FDA should begin a dialogue with industry and other

interested stakeholders on creating a guidance document to clarify and streamline the approval process for prevention products. As part of this effort, FDA should seek to make better use of surrogate endpoints, since this will shorten development times and get needed medicines to patients in a timely manner.

HHS can also spur innovation into prevention by ensuring that preventative treatments and diagnostics are reimbursed at appropriate levels by insurers and government programs. Current payment policies and delivery systems often discourage adoption of preventive therapies through misaligned payment incentives and other barriers. Yet preventative therapies often are highly cost-effective in the long run, avoiding expensive treatment procedures, such as surgery and hospitalization, that many patients otherwise would need to undergo if they were not taking prevention products. HHS should encourage reimbursement policies that support effective delivery of preventive innovations, which improve quality of care and yield long-term savings in treatment costs.

5. Establish Payment Policies That Support Innovation

A number of articles identify current payment policy as a significant barrier both to diffusion of innovation and access to recommended care. More research is needed on specific aspects of payment policy that impede diffusion of innovation and access to quality care.

Coye et al. point to suboptimal use of information technology and "a reimbursement system that fails to provide coverage for innovative technology in a timely manner" as impediments to health care quality improvement. *The Tipping Point and Health Care Innovations: Advancing the Adoption of Beneficial Technologies*, Molly Coye, MD, MDP, et al., The Health Technology Center, Commissioner Paper Synopsis, Accelerating Quality Improvement in Health Care conference proceedings, National Institute for Health Care Management and National Committee for Quality Health Care, Jan. 27-28, 2003, Washington D.C.

At a 2001 conference sponsored by the National Academy of Sciences, reimbursement policies were identified as a key public policy barrier to innovation in health care. For example, Dr. Mark McClellan, then a nominee to the president's Council of Economic Advisors, suggested at the conference that current reimbursement incentives created a barrier to adoption of computer technology by hospitals and other

institutions. *Medical Innovation in a Changing Healthcare Marketplace: Conference Summary*, National Academy of Sciences., Appendix C, p. 64.

In addition, in its report *Crossing the Quality Chasm: A New Health System for the 21st Century,* the Institute of Medicine's (IOM) Committee on Quality of Health Care in America concluded that "current payment methods do not adequately encourage or support the provision of high quality care." *Crossing the Quality Chasm: A New Health System for the 21st Century,* Institue of Medicine, Washington, D.C., National Academy Press, 2001.

The IOM report recommends research to identify the scope of services and interventions across the continuum of care needed by patients with priority diseases and conditions. HHS' FY 2006 research priorities under Section 1013 of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA) should adopt this recommendation. Identifying these services and interventions can help improve coordination of patient care and better align health care payment and organization with the needs of patients with priority diseases and conditions.

As highlighted in *Crossing the Quality Chasm*, current payment methods often discourage adoption of innovative, quality-improving delivery systems as well as innovative technologies. The report states that "[i]t is critical that payment policies be aligned to encourage and support quality improvement." The report continues that "[m]ost payment methods have an objective of cost containment or reflect consideration of issues of access" but "do not have the explicit goal of ensuring quality care or facilitating quality improvement."

The report recommended that private and public purchasers "examine their current payment methods to remove barriers that currently impede quality improvement, and to build in stronger incentives for quality enhancement."

Access to pharmaceutical innovation represents one important aspect of quality improvement, and we believe there are opportunities both to address current barriers to development and dissemination of innovative medicines and avoid creation of new barriers in Medicare policy. These include:

- Reliance on choice and competition: One of the ways that the federal government can impede development of and access to valuable innovations is by seeking to render up-front determinations about the value of individual

advances. While CMS must make decisions at the population level, the value of advances in medicine varies among individual patients and evolves as the role of the test or treatment evolves. CMS determinations about the value of new medicines or other medical technologies could prevent many beneficial advances from ever reaching patients. We encourage HHS to look to decentralized approaches wherever possible that are patient-centered and competition based.

- Recognition of the importance of incremental innovation: Incremental advances, such as newer medicines in a therapeutic class or improved models of pacemakers or hip implants, are a basic mechanism of all technological innovation. Newer medicines in a therapeutic class, for example, often have fewer side effects or greater ease of use that facilitates improved patient compliance. Incremental advances also lead to increased price competition, which can help contain costs. Medicare should pursue policy approaches that support continued development of incremental advances in medicine.

- Improving the timeliness and openness of CMS coverage, coding and payment decisions: Analysis of Medicare national coverage decisions completed for pharmaceuticals shows that CMS has taken an average of 377 days to make and implement coverage decisions on the national level. If CMS adopts excessive new coverage requirements, it would exacerbate these delays and discourage development of new therapies. We appreciate steps CMS is taking to improve the timeliness and openness of these procedures, and we look forward to working with the agency in this area.

- Keeping pace with innovation in technology: As innovation transforms the practice of medicine and delivery of health care, Medicare payment policy must adapt as well. The emerging field of personalized medicine, for example, offers opportunities for more effective, efficient delivery of care to many patients. Yet it also will challenge regulatory and payment policies, which are based upon current medicine and medical technology. If the health care system is to secure the full benefits of personalized medicine, governmental and private payers must have coverage and payment policies that support the timely adoption of new personalized medicine technologies.

- Keeping pace with innovation in health care delivery: Innovative approaches to health care delivery like disease management and coordinated care programs

can help provide more effective and efficient care for many patients. However, payment policy and other aspects of our health care system often discourage adoption of these types of programs. HHS should support policies that encourage adoption of disease management and similar approaches to patient care.

6. Educate The Public and Policymakers On Challenges To Innovation

As HHS knows, there is no guarantee for innovation. It requires dedication, hard work, resources and a willingness on the part of industry to accept significant risks. And perhaps most of all, it requires public policies that create a favorable environment for innovation.

Unfortunately, there is little understanding among the public and policymakers of the fragile nature of medical innovation, and the uncertainty and expense associated with pursuing it. HHS can play an important role in protecting and spurring future innovation by educating the public and policymakers about the drug discovery process and the need for policies that encourage innovation. This will help ensure that the U.S. retains and encourages policies that support continued leadership in medical innovation. Without innovation-friendly public policies, few other HHS policies intended to spur innovation are likely to bear fruit.

We thank you for your consideration of these comments.

Sincerely,

Scott M. Lassman
Assistant General Counsel